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Regressão da Remodelagem Ventricular Esquerda no Contexto de Estenose Válvular Aórtica

Regression of Left Ventricular Remodeling in the context of Aortic Valve Stenosis

março, 2017

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Regressão da Remodelagem Ventricular Esquerda num contexto de Estenose aórtica

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INTRODUCTION

BACKGROUND AND OBJECTIVES

The 2012 ES/EACTS Guidelines on the Management of Valvular Heart Disease recommend surgical aortic valve replacement to severe aortic stenosis (AS) patients who: 1) display any symptoms related to AS; 2) will undergo coronary artery bypass graft or surgery of the aorta or another valve; 3) are asymptomatic but present with systolic LV dysfunction (Left Ventricle Ejection Faction (LVEF)<50%) not attributable to any other cause and 4) are asymptomatic but display abnormal exercise test showing symptoms on exercise clearly related to AS[1]. However, recent studies have shown that a more proactive treatment strategy promoting surgery before the onset of symptoms may bring greater benefit[2]. The objective of this paper is to review currently existing literature in order to investigate the relationship between left ventricular remodeling, prognosis and therapeutic outcomes in AS, and to determine the potential thereof in recommending more proactive surgical approaches to asymptomatic patients. The bibliographic research conducted is summarized in figure 1.

DEFINITION OF AORTIC STENOSIS AND ITS SEVERITY

Aortic stenosis is a pathologic narrowing of the aortic valve characterized by a restricted outflow from the left ventricle into the aorta. AS is both a common and serious cardiovascular pathology[3] as it causes a significant increase in both mortality and morbidity of affected individuals[4]. The restriction of left ventricular outflow increases afterload and interferes with left ventricular function, promoting a series of changes in the heart, including left ventricular remodelling[5]. Being a common pathology whose incidence increases with age, it stands to reason that the disease burden it provokes in the developed world will increase over time, given population ageing[3,6], which reinforces the need to better understand the pathophysiology of AS.

A multifactorial etiology, with a complex interaction of anatomical, clinical and genetic factors, contributes to the genesis of AS.[7] AS' initial pathophysiology resembles that of atherosclerosis, with a significant overlap of risk factors for both diseases[8,9], followed by a calcification and propagation stage, where a complex process of fibrosis occurs, culminating with the calcification and narrowing of the valve and obstruction of left ventricular outflow.[10]

Roberts *et al* studied the natural history of 260 AS patients not subjected to surgical treatment over 50 years. This author reported that heart failure, angina pectoris or syncope, were overwhelmingly common (68% of men and 67% of women); that the onset of any cardiac symptomatology was associated with an exceptionally dire prognosis, supporting a median survival of 20 months after symptom onset; and that patients with cardiac symptomatology were at higher risk for death from cardiac events (both sudden and non-sudden) when compared to the asymptomatic group (OR: 3.61).[11]

The therapeutic gold standard for AS is aortic valve replacement (AVR), as confirmed by numerous studies demonstrating dramatic symptomatic relief and improvement of long-term survival[12]. An alternative to surgical replacement is transcatheter aortic valve implantation (TAVI), especially for patients with high surgical risk who cannot undergo surgical aortic valve replacement (SAVR)[13]. As far as medical therapy is concerned, no therapeutic regimen has been able to convincingly delay the progression of AS or reduce mortality once symptoms are established, and thus, it is limited to patients who require pre-surgical stabilization or for symptomatic management in patients who cannot or who choose not to undergo SAVR or TAVI.[14–16]

The 2012 ES/EACTS Guidelines on the Management of Valvular Heart Disease defined severe AS as having a valve area under 1 cm^2; an indexed valve area under 0.6 cm^2/m^2; a mean gradient greater than 40mmHg; a maximum jet velocity over 4.0 m/s; and a velocity ratio under 0.25[1]. The American Heart Association Guidelines for the Management of Patients with Valvular Heart Disease[17] define four main stages of AS, summarized in *Table 1*. Mild LV dysfunction can be observed as early as stage B and LV remodeling as early as stage C. The distinction between these stages is made primarily through the presence of symptomatology, the aortic valve morphology and area, the pressure gradient between the LV and the aorta, and the LVEF.[18,19] These latter 3 parameters are determined through echocardiographic studies, which are the cornerstone of AS staging[18,19], although other imaging procedures may also have a diagnostic role.[20,21]

It is important to distinguish between the various stages of the pathology, given the heavy implications upon prognosis and therapeutic decisions.[22,23] The decision to submit the patient to surgical treatment is based on a risk-benefit assessment of surgical risk associated with the procedure weighed against the risk posed by the lack of surgical correction. The current ES/EACTS guidelines[1] and AHA guidelines recommend against routine aortic valve replacement for asymptomatic patients on the basis that these

patients possess a low risk of cardiac sudden death (>1%) when compared to age-matched controls[17]. The indications for AVR according to ES/EACTS guidelines are summarized in *Table 2*.

LEFT VENTRICULAR REMODELLING IN THE CONTEXT OF AORTIC STENOSIS

Ventricular remodeling comprises the functional and anatomic changes undergone by the heart in response to either physiological stimuli, like exercise[24], high altitude[25], pregnancy[26] or to various pathological stimuli, like volume overload, as in valvular regurgitation,[27] pressure overload, as in AS,[28]or other situations where a more complex forms of overload may be present, like acute myocardial infarction (AMI)[27].

Various classifications exist for LVR and LVH. Verma *et al*, in the VALIANT study, defined 3 types of LVR: concentric remodeling, concentric hypertrophy and eccentric hypertrophy.[29] Khouri et al suggested an expansion of this system with subgroups for each category, namely indeterminate eccentric, dilated eccentric, thick concentric and thick and dilated concentric LVH.[30] Situations of volume overload tend to produce eccentric hypertrophy[26], whereas situations of pressure overload tend to produce concentric hypertrophy.[28]

AS imposes a chronic high afterload to the left ventricle, triggering compensatory changes aimed at reducing wall stress and maintaining cardiac output. The LV undergoes an increase in both relative wall thickness (RWT) and LV Mass Index (LVMi), which is the LV Mass (LVM) adjusted to body surface area (BSA)[29], in what is known as concentric hypertrophy. The increase in LVM negatively affects the contractility of heart[31]. However, the increase in afterload is not the only mechanism involved in LVH in the context of AS. Indeed, LVH is a complex, multifactorial process, modulated by variables such as gender[32], neurohumoral activation[18], and the association of AS with various comorbidities, like obesity and hypertension[33].

The aforementioned changes in LV wall thickness and geometry[34] occur simultaneously to a fibrotic process where myocardial areas of apoptosis are replaced by fibrosis[35], with the occurrence of a pathological sequence of progression from myocyte hypertrophy, to apoptosis, to fibrosis[36], with correspondent fibroblast recruitment and increase in fibrotic content of the myocardium[37]. The predominant pattern of fibrosis occurring in the context of AS is midwall fibrosis and its presence is

usually established via Late Gadolinium Enhancement (LGE) in a cardiac MRI[38]. The exact trigger for apoptosis in these circumstances is unknown, but both direct mechanical factors, such as wall stretch, and angiotensin II appear to play a relevant role[39–41]. This increase in myocardial fibrotic content ultimately produces a worse prognosis, due either to worsening of diastolic function[33] or to the increased arrythmogenic potential of the fibrotic heart[42] and cardiac sudden death[43,44]. The increased cardiac wall stress promotes an increase in circulating natriuretic peptides, particularly N-terminal B-type natriuretic peptide (NtBNP), as it appears capable of predicting symptom free survival and post-operative outcomes[45]. Myocardial ischemia is also a relevant process in LVH. It occurs mostly as the microvasculature of the heart becomes unable to keep up with the growing metabolic demands of the left ventricular mass[46], and thus, may also be a relevant contributor to the increasing fibrosis of the myocardium. Reflecting the influence of myocardial cell death in this process, higher circulating levels of cardiac troponins can be found, particularly with the usage of high sensitivity assays.[47]

While these changes are initially adaptive, with chronicity they tend to become maladaptive[48] and thus, LVH has a significant impact on the prognosis of AS, being an independent determinant of higher mortality and morbidity from cardiac events.[27,49–51]

LEFT VENTRICULAR REVERSE REMODELLING AFTER AORTIC VALVE REPLACEMENT

LV Reverse Remodeling (LVRR) is seen in AS patients who successfully undergo AVR, both with SAVR techniques or TAVI techniques[52] , defined as a normalization of LVMi, RWT, and other measurements of hypertrophy as well as recovery of cardiac function[53].

However, LVRR is frequently incomplete. Gavina *et al*[54]studied the presence of residual LVH in a post-SAVR setting, and observed that, in this cohort, 44% of patients maintained some degree of LVH after valve replacement, and that this incomplete regression heralded a worse prognosis, especially for women. Magalhães *et al*[55] performed a similar analysis regarding extension of the LVRR process in a TAVI setting and reported partial or complete normalization of LVMi and RWT in 24% of the population at 1 year follow-up post-TAVI, without a corresponding normalization of left atrial dimensions. In TRITON trial, Haverich *et al*[56] reported a mean reduction of 14% in LVMi at 1 year follow-up, and a 16% reduction at 3 years after surgical treatment of AS with a Next Generation Surgical Aortic Valve.

Similarly to the extent of LVH, LVRR is modulated by various factors apart from successful AVR. Hypertension appears to play an exceedingly important role, as those AS patients without hypertension who undergo AVR have a much greater amount of LVRR when compared to those with hypertension independently of total afterload[32].Prosthetic-patient mismatch[57] is also independently associated with a negative impact on the extent of LVRR[58], as demonstrated in a large cohort of AS patients by Del Rizzo *et al*[59]. Gender also has an impact, with women having a tendency towards more complete LVH regression when compared to men[60,61].

POSITIVE OUTCOMES ASSOCIATED WITH EARLIER SURGICAL INTERVENTION

Growing evidence begins to suggest, however, that surgical treatment strategies may effectively provide greater benefit to asymptomatic patients than previously believed.

In a prospective study conducted over 10 years, Kang *et al* studied patients with asymptomatic severe AS randomized between two treatment groups, one treated with early surgery, as defined as elective surgery performed before formal indication per the most recent available guidelines, and one treated with the conventional treatment strategy. The authors reported a cardiac and all-cause risk of death of 0% and 6% in the early surgical treatment group, and a 24% and 32% risk for the same variable in the conventional treatment group, over a median follow-up period of 1501 days. Authors concluded that the benefits of early surgery outweighed all the risks, and thus, that it was an option for the asymptomatic very severe AS patient. Also this group presented more LVH regression and better LV systolic function in post-op echocardiographic studies, indicating that early surgery is able to prevent irreversible myocardial damage and fibrosis, and therefore reduce the risk of cardiac sudden death. [62]

In 2015, Taniguchi *et al* analyzed data from a large multicenter registry to compare long term outcomes of patients with asymptomatic severe AS who were treated with AVR (SAVR or TAVI) at diagnosis and those managed with traditional conservative strategies. The authors reported dire outcomes in the group managed with the currently recommended conservative strategy when compared to those who underwent AVR, with a cumulative 5-year incidence of death by all causes of 26.4% vs. 15.4% (p=0.009); a cumulative 5-year incidence of cardiovascular and aortic valve related death of 18.6% vs. 9.9% (p=0.01); and a cumulative 5-year incidence of sudden death of 5.8% vs. 3.6 % (p=0.06) thus concluding that the

dismal outcomes associated with conservative treatment strategies for severe asymptomatic AS patients are largely surpassed by earlier AVR[2]

The AVATAR prospective, multicenter, randomized, controlled, parallel group, event-driven trial began in 2016 and aimed to evaluate the safety and efficacy of elective AVR for asymptomatic AS patients with preserved LVEF. To achieve this goal, a cohort of 312 asymptomatic patients with isolated AS and preserved LVEF will be randomized to one of two groups, one managed with the currently recommended strategy (medical treatment until symptoms arise or LVEF drops below 50%) and one to be treated with elective AVR. The primary outcome of the study is a composite variable of all-cause death, acute myocardial infarction, stroke or unplanned hospitalization for heart failure. Secondary outcomes will include a safety analysis to determine whether the early surgery group suffers from any increase in operative and in hospital mortality, or from an increase in valve related complications, when compared to patients operated after symptom onset.[63] This trial will definitely contribute to expand the knowledge about the best timing for AVR.

POSSIBLE ROLE OF LVR AND LVH FROM A THERAPEUTIC AND PROGNOSTIC STANDPOINT

This review of current information, summarized in *Table 3,* regarding LVH in the context of AS revealed a large amount of relevant information that can potentially be utilized to support the inclusion of LVH in operative criterion for AS.

Regarding echocardiography, data exists supporting an expansion of the hemodynamic characteristics evaluated[64], and the usage of Integrated Backscatter (IBS)[65] techniques, which are a form of echocardiographical characterization of myocardial tissues, shows great promise. Cyclic Variation of IBS (CVIBS), mean IBS at end diastole (IBSed), and mean Cyclic Variation of IBS index (CVIBSi) have value as predictors of LVRR in a post-AVR setting: CVIBS showed a sensitivity of 84.6% and specificity of 63.1%. using values equal to or greater than 5.1 dB as a cut- off. IBSed showed a sensitivity of 84.6% and specificity of 78.9% using values equal to or greater than 34 dB as a cut-off. CVIBSi showed a sensitivity of 79.5% and specificity of 84.2% using values equal to or greater than 15.7% as a cut-off[66]. Echocardiographic strain measurements have also shown potential. Two-dimensional back longitudinal scatter shows a strong association with adverse outcomes for the asymptomatic AS patient, when values

lower than 13% are found,[67] and 3 dimensional global longitudinal strain has a sensitivity and specificity of 76% and 77%, for a cutoff value of -14.5 for predicting MACE, also in asymptomatic AS patients.

The usage of MRI also shows potential for expansion. LGE; as said above, is the quintessential method for evaluating the midwall myocardial fibrosis occurring in LVH. LGE and LVMi share an independent association with plasma cTnI concentrations[68], and LGE is also independently associated with the aforementioned echocardiographic strain measurements[69]. Midwall fibrosis as measured by LGE in an MRI appears associated with an 8 fold increased risk of all-cause mortality in moderate to severe AS patients[38].

The common electrocardiogram also shows interest, as measurements of LVH and LV strain have a direct, independent relationship with prognosis[70].

Perhaps the most interesting data comes in the domain of biomarkers. The usage of high sensitivity cardiac Troponin T (hs-cTnT) assays is particularly relevant, as high circulating titers of hs-CTnT are associated with poor prognosis even in asymptomatic AS patients[71], namely cardiovascular death or need for future AVR[68]. B-type Natriuretic Peptide (BNP) is also relevant. Lower levels of NT-BNP correlate with higher magnitudes of LMVi normalization and better quality of life in a post-AVR setting[72]. In a groundbreaking study, Gárcia *et al*[73] demonstrated the potential relevance of titers of miR-133a in the timing of the surgical decision for AVR, as higher titers of pre-operative circulating miR-133a revealed greater potential for LVMi normalization post-op.

DISCUSSION

LIMITATIONS OF CURRENT GUIDELINES

As of today, the usage of LVH and markers thereof is sparse for therapeutic decision in the context of AS. While the 2012 ES/EACTS[1] guidelines already include LVH when recommending AVR for asymptomatic patients, with normal exercise testing, low surgical risk and an excess of LVH in the absence of hypertension, the class of recommendation is only IIB, and the contemporary 2014 AHA guidelines[17] make no reference whatsoever to these potentially useful markers.

The current management strategy recommended by both European and American guidelines is also a subject of controversy, with large, multi-center studies showing the currently recommended strategy of "watchful waiting" prompts a dismal outcome.

With this in mind, several studies have attempted to uncover other parameter that might help to clarify the best time for ABR. For instance, in 2012, Carabello recommended AVR for asymptomatic AS patients with either a positive exercise test; heavy valve calcification; documented rapid progression of AS from serial measurements; excessive left ventricular hypertrophy; or rising natriuretic peptides,[74] differing from the established guidelines.

Various studies found that the persistence of LVH in a post AVR or TAVI setting is associated with worse outcomes, like an increase in risk of MACE, all-cause death, or cardiac re-hospitalization. There appears to be a trend showing that while men more frequently exhibit maladaptive cardiac remodeling when compared to women, women have a worse prognosis in comparison to men when said remodeling is present[54].

All of these potentially useful markers of prognosis can be evaluated using studies which are already performed on a routine basis for AS patients (echocardiography, electrocardiography, blood measurements and MRI), and thus there would be virtually no impediment to the incorporations of these new measures in newer editions of the guidelines should their utility be confirmed.

However, to fully recommend a change in guidelines, more research is needed. It would be essential to determine whether earlier surgery is associated with better LVH regression and better prognosis. With this objective in mind, the AVATAR study[63] begun in 2016, will provide key information.

Either way, data shows that the risk-benefit analysis regarding surgical recommendation in asymptomatic AS is overly simplistic, overlooking various highly useful markers of prognosis. The construction on an integrated risk score for these patients, utilizing various prognostic markers apart from hemodynamic measurements, like echocardiographic LV strain and LVH, electrocardiographic LVH and LV strain, various biomarkers and MRI markers, could be integrated into future guidelines to recommend earlier surgery for asymptomatic AS patients with a particularly dire prognosis.

CONCLUSIONS

While further studies are essential to cement these conclusions, the weight of recent data appears to indicate that current guidelines present an overly simplistic risk-benefit analysis regarding the surgical decision for AS patients, and an overly passive and conservative approach to asymptomatic AS patients. The association of LVH, its echocardiographic translation, namely ECG strain, and various cardiac biomarkers, with the occurrence of MACE and prognosis even in asymptomatic patients herald great potential in the design of a newer, more complete integrated risk score for AS, which could reveal asymptomatic patients with an exceptionally dire prognosis and this, with great potential benefit from more proactive surgical interventions, as is illustrated in *Figure 2.*

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ANNEX: FIGURES

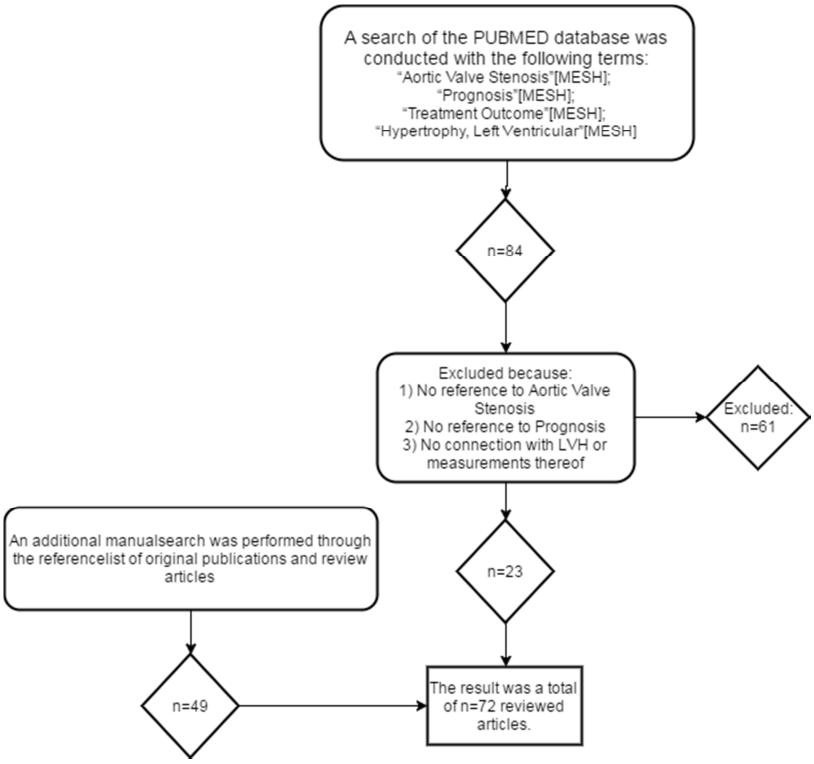

Figure 1 - Review flowchart

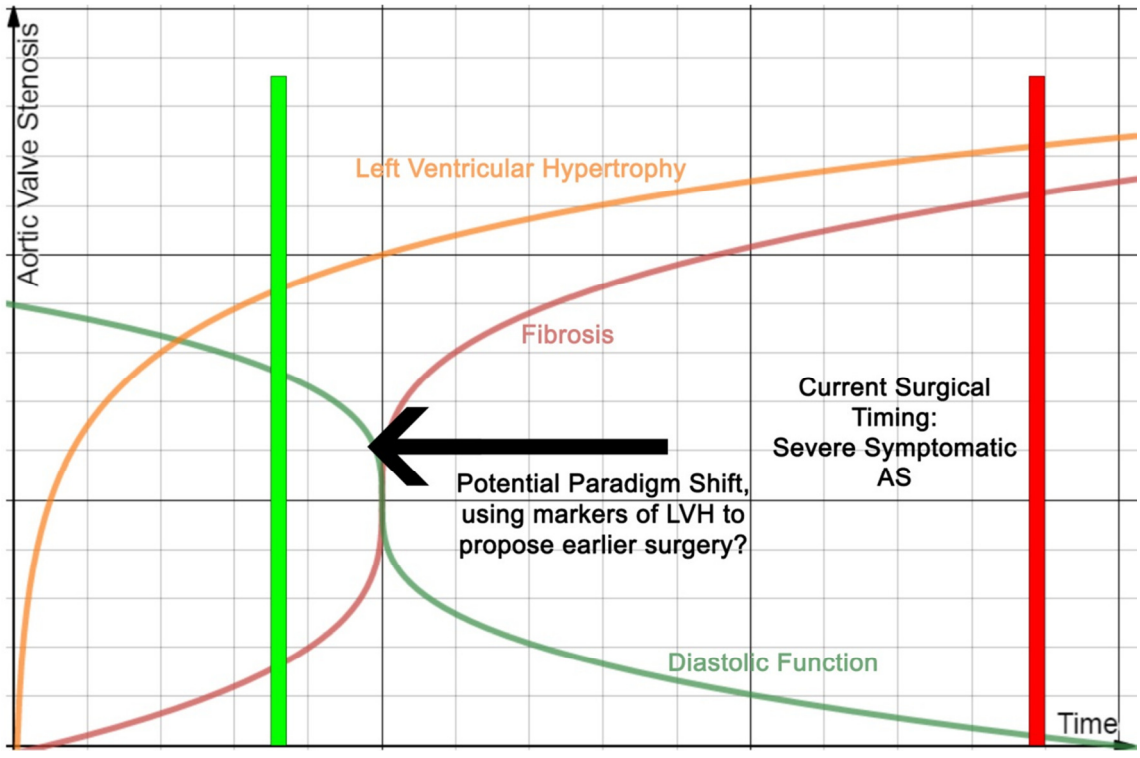

Figure 2 - The usage of markers of LVH could bring a paradigm shift in the surgical timing of AS.

ANNEX: TABLES

Stage	Definition
A	At Risk of AS
B	Progressive AS
C	Asymptomatic Severe AS
C1	Asymptomatic Severe AS
C2	Asymptomatic Severe AS with LV Dysfunction
D	Symptomatic Severe AS
D1	Symptomatic Severe High-Gradient AS
D2	Symptomatic Severe Low-Flow\Low-Gradient AS with Reduced LVEF
D3	Symptomatic Severe Low-Gradient AS with normal LVEF or Paradoxical Low-Flow Severe AS

Table 1 - Summary of AS Stages. *Adapted from AHA Guidelines for the Management of Patients with Valvular Disease.*[17]

Recommendations	COR	LOE
AVR is indicated **in patients with severe AS and any symptoms related to AS.**	**I**	B
AVR is indicated **in patients with severe AS undergoing Coronary Artery Bypass Graft, surgery of the ascending aorta or another valve.**	**I**	C
AVR is indicated **in asymptomatic patients with severe AS and systolic LV dysfunction (LVEF <50%) not due to another cause.**	**I**	C
AVR is indicated **in asymptomatic patients with severe AS and abnormal exercise test showing symptoms on exercise clearly related to AS.**	**I**	C
AVR should be considered **in high risk patients with severe symptomatic AS who are suitable for TAVI, but in whom surgery is favoured by a 'heart team' based on the individual risk profile and anatomic suitability**	IIa	B
AVR should be considered **in asymptomatic patients with severe AS and abnormal exercise test showing fall in blood pressure below baseline**	IIa	C

AVR should be considered **in patients with moderate AS undergoing Coronary Artery Bypass Graft, surgery of the ascending aorta or another valve.**	IIa	C
AVR should be considered **in symptomatic patients with low flow, low gradient (<40 mmHg) AS with normal EF only after careful confirmation of severe AS.e** **AVR**	IIa	C
AVR should be considered **in symptomatic patients with severe AS, low flow, low gradient with reduced EF, and evidence of flow reserve**	IIa	C
AVR should be considered **in asymptomatic patients, with normal EF and none of the above mentioned exercise test abnormalities, if the surgical risk is low, and one or more of the following findings is present: Very severe AS defined by a peak transvalvular velocity >5.5 m/s; Severe valve calcification and a rate of peak transvalvular velocity progression ≥0.3 m/s per year.**	IIb	C
AVR may be considered **in symptomatic patients with severe AS low flow, low gradient, and LV dysfunction without flow reserve.**	IIB	C
AVR may be considered **in asymptomatic patients with severe AS, normal EF and none of the above mentioned exercise test abnormalities, if surgical risk is low, and one or more of the following findings is present: Markedly elevated natriuretic peptide levels confirmed by repeated measurements and without other explanations; Increase of mean pressure gradient with exercise by >20 mmHg; Excessive LV hypertrophy in the absence of hypertension.**	IIB	C

Table 2 - Summary of Recommendations in AS: Timing of Intervention. COR, class of recommendation; LOE, level of evidence. *Adapted from the ESC/EACTS Guidelines on the Management of Valvular Heart Disease* [1]

Authors	Date	Aims	Population and Methods	Relevant Findings
Gavina *et al* [54]	2016	Evaluate whether residual LV hypertrophy is associated with clinical outcomes after AVR in severe AS.	In a prospective cohort of 132 patients with severe AS with a mean follow-up was 6.0 ± 1.5 years, clinical and	**Residual LVH** was present in 44% of patients after AVR. The **risk of all-cause death and non-fatal cardiovascular**

			echocardiographic parameters were evaluated in a pre-op and post-op setting. Clinical endpoints were all-cause death and combination of in all-cause death and non-fatal cardiovascular hospitalization. 56 random patients went biopsies during AVR for collagen volume fraction evaluation.	**hospitalization** was higher in patients with residual LVH. **Residual LVH** was associated with a **worse outcome** in women but not in men.
Debry *et al*[75]	2016	Evaluate the prognostic significance of LV concentric remodeling (LVCR) in the context of AS.	331 patients with AS and an LVEF > 50% were enrolled. The endpoints were mortality with conservative management and mortality with conservative and/or surgical management.	Among the patterns of LV geometry in AS, **LVCR** portends the **worst outcome**. Patients with LVCR and AS have a considerable increased risk of mortality, regardless of clinical management.
Güçlü *et al*[76]	2015	Investigate whether myocardial efficiency is reduced in patients with LVH caused by AS and to assess the effect of AVR on myocardial efficiency in relation to exercise capacity.	Echocardiography, cardiopulmonaryexercise test, positron emission tomography and cardiovascular MRI were performed in 10 AS patients before AVR and 4 months after AVR.	**Myocardial external efficiency** is significantly reduced in patients with AS-induced LVH, and it's improvement is an important predictor of AVR-induced improvement of exercise

			Fourteen healthy individuals served as control group.	capacity in AS patients.
Sjöberg *et al*[77]	2015	Evaluate electrocardiographic LVH criteria as a method of diagnosing and quantifying LVH in patients with AS undergoing TAVR.	24 patients underwent pre-TAVR electrocardiography and echocardiograph. The electrocardiographs were evaluated using the Sokolow–Lyon, Romhilt–Estes and Cornell Voltage criteria for LVH as well as spatial maximal QRS-T angle and 3D QRS maximal spatial vector. The LVM was measured by echocardiography.	There was no correlation between LVM and conventional electrocardiographic LVH criteria or spatial parameters. In TAVR patients, none of the ECG LVH criteria should be used for evaluation of LVM.
Carstensen *et al*[67]	2015	Compare velocity, via color Doppler tissue imaging and deformation via two-dimensional speckle-tracking echocardiography, in relation to global and regional longitudinal function in asymptomatic and severe symptomatic AS.	231 patients with aortic stenosis were divided into four groups: asymp-tomatic moderate AS; asymptomatic severe AS; and symptomatic severe aortic stenosis with preserved; and reduced LVEF.	Only **diastolic e0, longitudinal displacement**, and **basal longitudinal strain (BLS)** remained significantly associated with symptomatic status, independent of other factors. **BLS** has the strongest association with symptomatic status, and

				BLS <13% is related to adverse outcomes in severe asymptomatic AS.
Helske-Suihko *et al*[78]	2015	Ascertain whether candesartan, favorably influences LV structure and function and improves exercise capacity in AS patients.	51 patients with severe AS were randomized to receive candesartan or placebo. 8 patients discontinued treatment .43 patients underwent echocardiography, walking test, and measurement of Nt-proBNP before and after an average of 5-month treatment.	Candesartan was well tolerated but **had no favorable effects** on the anatomy of the LV or effort tolerance.
Tan *et al*[64]	2015	Evaluate the incremental predictive value of a complete echocardiogram in identifying high-risk surgical candidates in a pre-op setting.	432 patients with a mean age of 73.5 years and 38.7% females were subjected to a full preoperative echocardiographic study, which was evaluated to quantify chamber size and function and valve function.	Cox regression revealed 5 echocardiographic predictors of all-cause mortality: **small LV end-diastolic cavity size**; **LV mass index**; **mitral regurgitation grade**; **right atrial area index**; **and mean aortic gradient <40 mm Hg.**
Gerdts *et al*[79]	2015	Assess the impact of echocardiographic LV mass on the rate of major cardiovascular events in asymptomatic AS	1656 patients (mean age, 67 years; 39.6% women) with mild-to-moderate asymptomatic aortic stenosis participating in	**Higher baseline LVMi** independently predicted increases of 12% for major cardiovascular events,

		patients.	the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study were followed during 4.3 years of randomized treatment with combined simvastatin 40 mg and ezetimibe 10 mg daily or placebo.	28% for ischemic cardiovascular events, 34% for cardiovascular mortality, and 23% for combined total mortality and hospitalization for heart failure (all P<0.01). **Higher LVMi** is independently associated with increased cardiovascular morbidity and mortality during progression of aortic stenosis.
Magalhães *et al*[55]	2015	Describe the remodeling process in patients with severe AS who underwent TAVI.	Echocardiographic data was collected at baseline, 30 days, 6 months, and 1 year, from a cohort of 333 patients who underwent TAVI. Patients were categorized according to LVMi and RWT to one of the four common typologies of LVH. Reverse remodeling defined as normalization of LVMi and/or RWT and adverse remodeling as an increase in LVMi and/or RWT.	**Reverse LV remodeling** was observed in 24% of patients. TAVI **reverses ventricular remodeling** and LV hypertrophy induced by AS, although **incompletely**, and this reversal is not followed by a change in left atrial dimensions. The clinical impact of these findings is unclear.

Nagata *et al*[80]	2015	Determine which echocardiographic LV strain component was the most powerful predictor of major adverse cardiovascular events in severe asymptomatic AS patients.	104 patients with severe asymptomatic AS were followed for a median follow-up of 374 days, and studied with 2-dimensional speckle tracking echocardiography and 3-dimensional speckle-tracking echocardiography and recording any major adverse cardiovascular events.	**3-dimensional global longitudinal strain** is the strongest index for predicting future major adverse cardiovascular events, with a sensitivity and specificity of 76% and 77%, for a cutoff value of -14,5%. In a univariate analysis, the **LVMi** also had a statistically significant association with said events.
Petrov et al[81]	2014	Study the prognostic impact of maladaptive remodeling in a post-AVR setting.	128 patients who underwent AVR for AS were echocardiographically studied at the moment of surgery and 4 years later	Men more often exhibited **maladaptive LVH**, with increased fibrosis and levels of cardiac fibriosis biomarkers. The presence of **maladaptive LVH** in women was associated with worse survival.
Beach *et al*[82]	2014	Understand the factors modulating LVRR after AVR, the relationship between the preoperative symptoms and modulators of left heart remodeling, and their	Over 17 years, 4264 patients underwent primary aortic valve replacement for aortic stenosis. Changes in the time course of LV reverse remodeling were	**LVH** rapidly declined after surgery, and remained relatively constant but greater than the upper limit of normal. The most important risk factor for residual **LVH**

		influence on long-term survival.	assessed using 5740 post-op TTE from 3841 patients.	was greater preoperative **LVH**. Other factors included a **greater left atrial diameter**, a lower **ejection fraction**, and **male gender**. **Preoperative severe LVH** and **left atrial dilatation** reduced long-term survival, independent of symptom status. **Severe LVH with left atrial dilatation** can develop from severe **AS**, even without symptoms. These changes can persist after AVR, and are associated with decreased long-term survival.
Haverich *et al*[56]	2014	Analyze the intermediate-term follow-up data from a large series of patients enrolled in the Surgical Treatment of Aortic Stenosis With a Next Generation Surgical Aortic Valve trial.	287 patients with AS underwent rapid deployment aortic valve replacement using a stented trileaflet bovine pericardial bio-prosthesis. Core laboratory echocardiography was performed at baseline, discharge, and 3 months, 1 year, and 3 years post-	At 1 year, **LVMi** had decreased by 14% and at 3 years by 16% compared with the discharge. Future studies will establish whether these favorable structural changes correlate with improvement in long-term survival and functional status

			op.	
Chin *et al*[68]	2014	Assess prognostic value of high sensitivity troponin I concentrations in AS as a marker of advanced LVH and predictor of adverse prognosis	122 patients with AS underwent ECG, echocardiography, and MRI, assessing LV mass, function and fibrosis. 131 patients were followed for a median of 10,6 years to assess the outcomes.	The **LVMi** and **late gadolinium enhancement** were independently associated with **cTnI** concentrations. **Plasma cTnI concentrations** were associated with a hazard ratio of 1.77 for cardiovascular death or AVR, independent of age, sex, systolic ejection fraction, and aortic stenosis severity
Gavina *et al*[32]	2014	Evaluate the impact of hypertension on the left ventricular mass regression in AS after AVR.	135 patients with severe aortic stenosis were studied at baseline and 1 year post-op. In 32 patients we analyzed myocardial gene expression of collagen types I and III, connective tissue growth factor, transforming growth factor-β1, metalloproteinase-2 and its tissue inhibitor and compared its levels vs controls.	**Mass regression** was significantly higher in patients **without hypertension**, with a median decrease of 25.9% vs 5.4%. AS patients had increased expression of collagen types I and III. Hypertensive patients had higher relative expression of collagen type I vs III and TIMP2 expression was up-regulated and correlated with higher baseline LVMi.

Lindman et *al*[72]	2014	Examine the relationship between left ventricular mass regression and clinical outcomes after TAVR.	2115 patients with symptomatic AS at high surgical risk receiving TAVR in the PARTNER randomized trial or continued access registry. Clinical outcomes were compared for patients with greater than vs. lesser than median percent change in LVMi .	**Greater LVMi regression** was associated with similar rates of all-cause mortality, but **significantly lower rates of rehospitalization** (for all causes, 9.5% vs. 18.5%; and specifically for heart failure 7.3% vs. 13.6%) **lower levels of BNP** and a **trend towards better QoL**, when compared to those with lesser regression.
Shah *et al*[69]	2014	Investigate the mechanisms and outcomes associated with LV ECG strain in a context of AS.	To investigate mechanism, 102 patients were studied via electrocardiography, echocardiography, and cardiovascular MRI. T1 mapping was used to determine diffuse fibrosis and late gadolinium enhancement to determine replacement fibrosis. To investigate outcomes, 140 patients were followed for a median of 10,6 years.	**LGE of the midwall** was present in all patients with ECG strain, with positive and negative predictive values of 100% and 86%, respectively, leading to the conclusion that **ECG strain is a specific marker of cardiac midwall fibrosis**. Patients with ECG strain had **greater increases of LVMi**, **higher high-sensitivity plasma cardiac troponin-I concentrations**, **more**

				severe AS, and an **increase in diffuse myocardial fibrosis**, when compared to those without ECG strain. ECG strain was found to be an **independent predictor of cardiovascular mortality or need for later AVR.**
Ben-Dor *et al*[83]	2013	Assess the relationship of BNP with AS severity and prognosis.	289 high-risk patients with severe AS who were referred for TAVI. Patients were divided into tertiles based on BNP level (I, II, III), were followed for a median of 319 days, range 110 to 655.	The **degree of AS** did not differ among the 3 groups. **Mortality rates** during a median were significantly lower in Group I compared with Groups II and III. However, **BNP levels** did not have an **independent association** with mortality when adjusted for co-variables. At 1-year follow- up post TAVI, the **mean BNP level** decreased significantly.
Mannacio *et al*[84]	2013	Evaluates BNP as a marker of LV diastolic dysfunction and the relationship between BNP values and the grade of LV diastolic	113 AS patients with preserved LVEF who underwent AVR were evaluated preoperatively, 5 days post-operatively and at 12-month follow-	**BNP** values correlated with the degree of diastolic dysfunction. BNP level of 120 pg/ml were 91% sensitive and 85% specific for diastolic

		dysfunction.	up, via echocardiography, to assess LV dimensional and functional parameters, with concomitant measurements of BNP.	disease, while 300 pg/ml was 80% sensitive and 91% specific for moderate or severe diastolic dysfunction. 12 months after AVR, **BNP** values were **strongly correlated** with the significant echocardiographic parameters suggestive of diastolic dysfunction.
La Manna *et al*[85]	2013	Investigate the degree of reverse remodeling of the LV and changes in function thereof six months after TAVI via cardiac MRI.	27 patients, with a mean age of 80.7±5.2 years, had paired cardiac MRI at baseline and at 6-months post-op, measuring LVMi, end diastolic volume indexed to body surface area LVEF and stroke volume.	Cardiac MRI demonstrates significant regression of LVH at 6-months post TAVI.
Garcìa *et al*[73]	2013	Asses the significance of plasma myocardial micro RNA 133a, as a biomarker capable of predicting LVH reversibility in post-AVR patients	74 aortic stenosis patients. miR-133a expression evaluated in LV biopsy. Circulating miR-133a measured in peripheral and coronary sinus blood. LV mass reduction determined echocardiographically	**Levels of miR-133a** in the myocardium and in the plasma were directly correlated. **Preoperative titers of miR-133a** were higher in those whose LV mass normalized after 1 year. **miR-133a** has great

				potential for the decision of surgical timing, particularly for asymptomatic patients.
Eleid *et al*[86]	2013	Study the relevance of flow gradient patterns in Severe AS with preserved LVEF.	1704 consecutive patients with severe AS and preserved ejection fraction using 2-dimensional and Doppler echocardiography	Low flow\low gradient AS has a poorer prognosis compared to other variants of AS, particularly with a higher incidence of atrial fibrillation and heart failure and with higher rates of mortality. In low-flow\low-gradient AS, **smaller LVMi** (99±30 vs 112±27 , p<0.05) and **smaller RWT** (0.49±0.08 vs 0.53±0.09, p>0,05) was observed in comparison to the classical variant of low-flow\high-gradient AS.
Breitenbach *et al*[21]	2012	Compare the decrease LVMi by MRI vs. transthoracic echocardiography after AVR for severe AS.	149 patients who underwent AVR. Transthoracic echocardiographic and cardiac MRI measurements of LVMi were made at baseline and at 6 months of follow-up and were	Because of the overestimation of the decrease in LVMi by the Devereux formula, as well as the higher accuracy and reproducibility of cardiac MRI measurements, the latter should be preferred to TTE.

			compared. Changes in mean pressure gradients were examined using transthoracic echocardiography.	
Flett *et al*[87]	2012	Determine the clinical significance of diffuse myocardial fibrosis in severe AS before and after AVR..	Severe AS patients underwent echocardiography, BNP, 6 min walk test, and and results equilibrium contrast cardiovascular magnetic resonance (EQ-CMR)pre-op, at baseline and at 6 months post-op. EQ-CMR was also performed in 30 normal controls	**Diffuse myocardial fibrosis** is elevated in severe AS. It correlates with functional capacity at baseline. **LV hypertrophy regression** 6 months after AVR occurs via predominantly cellular mechanisms.
Greve *et al*[70]	2012	Assess the prognostic value of left ventricular strain determined via electrocardiography, and LVH, assessed by Sokolow-Lyon voltage criteria and Cornell voltage-duration criteria, in the context of asymptomatic AS.	1533 patients participating in the SEAS study were followed for a median of 4.3 years. Primary end points were: first episode of myocardial infarction, nonhemorrhagic stroke, heart failure, aortic valve replacement, or cardiovascular death.	**ECG left ventricular strain** was associated with a **3,1** times greater risk of myocardial infarction, and that **ECG LVH** determined by both criteria was associated with a **2,5** times greater risk of either myocardial infarction, heart failure, or cardiovascular death.
Vizzardi *et al*[88]	2012	Investigate the effects of TAVI LVH and diastolic	135 patients who underwent TAVI had an	Significant **LVRR** measure by reductions in

		function in patients with severe AS.	echocardiographic and clinical assessment performed at baseline and at 6 months.	LV mass and LVMi, **associated with improvement in LV systolic and diastolic function** was found in patients with severe AS 6 months post-op.
Røsjø et al[71]	2011	Study the prognostic value and relation to echocardiographic indexes of cardiac function and anatomy of circulating hs-cTnT in AS.	57 AS patients with myocardial hypertrophy underwent echocardiographic study. hs-cTnT levels were linked to prognosis and echocardiographic indexes of myocardial structure and function	In moderate and severe AS patients, TnT levels are **universally detectable** using high sensitivity assays, LV mass and systolic function, are determinants of hs-cTnT levels; and **high hs-cTnT levels** are associated with a **poor prognosis**.
Dweck *et al*[38]	2011	Assess the prognostic significance of midwall and infarct patterns of late gadolinium enhancement in AS.	A total of 143 patients who underwent gadolinium contrast MRI were categorized into absent, midwall, or infarct patterns of LGE and were followed for 2 years.	**Midwall fibrosis** was associated with 8 times greater, and the **infarct pattern** with 6-times greater all-cause mortality, despite similar aortic stenosis severity and coronary artery disease burden. **Midwall fibrosis** and **ejection fraction** were independent predictors of all-cause mortality.

Cioff *et al*[89]	2011	Determine the prognostic impact of LVH in the context of asymptomatic severe AS.	209 patients had a complete clinical and imagiologic data after a median follow-up of 22 months.	LVH is common in patients with asymptomatic severe AS and is associated with an increased rate of cardiovascular events independent of other prognostic covariates.
Dahl *et al*[90]	2011	Study the relation of left atrial pressure overload in severe AS to ventricular remodeling and clinical outcome after AVR.	119 patients with severe AS scheduled for AVR were evaluated. Echocardiography was repeated 12 months after surgery. Patients were followed up for 24 months.	**Preoperative left atrial dilation** was associated with LVH and increased filling pressure. Preoperative **left atrial volume index** was associated with persistent abnormalities in left ventricular filling pressure and LVMi at 1 year after surgery. In patients with symptomatic severe AS undergoing AVR, **left atrial volume** provides important prognostic information beyond standard risk factors
Fijalkowski *et al*[66]	2010	Evaluate possible changes between pre- and post-op studies of echocardiographic	58 patients with AS. Average follow-up of 18 +- 5 months after AVR. Traditional transthoracic	**Significant regression** of LVH parameters, namely RWT, septum thickness and LMVi, were observed

		integrated backscatter (IBS) parameters of LV systolic and diastolic dysfunction and determine whether pre-op IBS parameters were capable of predicting post-op LV reverse remodeling.	echocardiography and analysis of IBS reflectivity were performed before AVR and during the control visit after AVR.	post-op, and a ROC under-the-curve showed that **CVIBS , mean IBSed, and mean CVIBSi** have similar capacities to predict LV reverse remodeling..
Stewart *et al*[91]	2010	Determine if tissue Doppler measures of LV systolic and/or diastolic function or echocardiographic LVH are useful for stratifying asymptomatic patients with severe calcific AS according to risk.	183 initially asymptomatic patients with moderate or severe AS and a normal LVEF were followed for median 31 months. Peak systolic and diastolic mitral annular velocities and LV mass were measured by echocardiography at baseline and during follow-up.	Tissue Doppler measures of LV systolic and diastolic function and LV mass **provide limited predictive information** after accounting for the severity of stenosis.
Villar *et al*[92]	2009	Determine whether plasma TGF-b1 relates with myocardial remodeling, reflected by LV transcriptional adaptations of genes linked to myocardial hypertrophy and fibrosis, and by heart morphology	39 AS patients who underwent AVR, 27 healthy volunteers; 12 mice subjected to transverse aortic arch constriction; and 6 mice who underwent sham surgery.	A **circulating TGF-b1**-mediated mechanism is involved, in both mice and humans, in the excessive deposition of extracellular elements and hypertrophic growth of cardiomyocytes under pressure overload.

		and function.		

Anexos

SPCCTV . NORMAS DE PUBLICAÇÃO DE TRABALHOS

A Revista da SPCCTV destina-se à publicação de artigos originais nos campos da Cirurgia Cardiotorácica e Vascular. Os manuscritos serão revistos pelos Editores e por revisores externos, e a sua aceitação dependerá do seu interesse, originalidade e validade científicas. A língua oficial da revista ‘e o Português, mas a submissão de Artigos Originais, Artigos de Revisão, Casos Clínicos e Imagens em Cirurgia integralmente em língua Inglesa ‘e fortemente recomendada. Caso desejem, os autores podem enviar uma versão em Inglês (para indexação) e outra em Português, para a revista impressa. E obrigatória a submissão dos resumos em Inglês.

ARTIGOS
São aceites submissões nas seguintes categorias:

Tipo de artigo	Limite de palavras	No máximo de autores	No máximo de referências	No máximo de tablas e figuras
Artigo Original	5000	8	25	8
Artigo de Revisão	s/ limite	8	s/ limite	s/ limite
Caso Clínico	1000	5	10	4
Imagens em Cirurgia	50	4	0	2
Carta ao Editor	850	4	8	2
Editorial	1000	2	10	2

A contagem de palavras deve incluir resumo e bibliografia, excluindo legendas e tabelas.

A cada edição, uma imagem seleccionada figura na capa da revista impressa.

Os editoriais apenas podem ser submetido mediante convite do corpo editorial.

As Cartas ao Editor, Imagens em Cirurgia e Editoriais dispensam o envio de Resumo.

FORMATACAO
A submissão devera ser feita integralmente em formato electrónico. Os ficheiros de texto devem ser submetidos em formato Word, com paginas numeradas no canto inferior direito, tipo de letra Times New Roman, tamanho 12, duplo espaço e justificados. As imagens devem ser submetidas em ficheiros individuais, em formato .tiff, com uma definição mínima de 300dpi.

ELEMENTOS OBRIGATORIOS

A. CARTA DE SUBMISSAO
Os manuscritos devem ser acompanhados de uma Carta de Submissão que terá de incluir:
- a declaração de originalidade,
- a concordância de todos os autores com o teor do artigo e aprovação da versão final,
- a transferência da propriedade intelectual para a Revista e,
- a declaração da presença ou ausência de conflitos de interesse. Se existentes, os Autores devem revelar as relações comerciais com tecnologias em estudo, as fontes de financiamento, a sua filiação Institucional ou Corporativa, incluindo consultadorias.

Nota: Os Autores poderão ser responsabilizados por falsas declarações.

B. PAGINA DE TITULO
Esta deve incluir o Título sem abreviações e em Maiúsculas; o nome e apelido dos autores e o(s) nome(s) e local(ais) da Instituição(ões) de afiliação de cada autor. O nome, endereço, telefone e email do autor correspondente, deve ser inscrito no fundo da página de título. No caso do manuscrito ter sido apresentado nalguma Reunião, esta deve ser discriminada juntamente com a data de apresentação. A contagem total de palavras do artigo (incluindo os resumos, mas excluindo tabelas, figures e referências) deve ser referida.

C. RESUMO (ABSTRACT)
O Resumo, por ser a secção mais lida de todos os artigos, é fundamental. Deve ser factual, sem abreviações (excepto unidades do SI). Deve incluir o Titulo e Autores, e ser estruturado em Objectivos – problema em estudo ou objectivo do estudo, Métodos, explicando como o estudo foi realizado, Resultados, revelando os dados encontrados e sua importância e Conclusão, revelando a conclusão do estudo. O limite máximo de palavras no resumo é 250.

D. TEXTO
O texto deve ser organizado nos seguintes elementos:

Introdução: deve revelar o objectivo da investigação e fazer uma revisão bibliográfica curta do estado da arte em relação ao problema em estudo.

Material e Métodos: estes devem ser descritos em detalhe com a informação adequada sobre Estudos Humanos ou Animais como atrás referido. O uso de abreviações deve ser limitado às unidades de medida do SI ou às de uso comum. As tecnologias devem ser nomeadas através do seu nome genérico, com o seu nome comercial, nome e local do fabricante entre parêntesis. As técnicas estatísticas de analise de dados devem ser descritas em detalhe.

Resultados: estes devem ser considerados a parte mais importante do artigo. Por tal, é importante que sejam descritos de forma concisa mas simultaneamente realçando os todos os resultados de forma completa, através de tabelas ou figuras, incluindo os comentários dos autores no texto.

Discussão: a discussão, deve ser clara e breve, devendo incluir a interpretação da significância dos resultados e da sua relação com outros trabalhos publicados na mesma área. A importância dos resultados e as limitações metodológicas, se existirem, devem ser enunciadas.

Agradecimentos: a existirem, devem ser referidos no final do texto

Referências: devem ser apresentadas sequencialmente de acordo com a ordem de uso no texto e apresentadas como números entre parêntesis rectos. Comunicações pessoais e dados não publicados não devem ser incluídos na lista de referências, embora possam ser referidos no texto. Nas referências todos os autores devem ser referidos e os jornais ou revistas apresentados de acordo com as abreviações usadas no Index Medicus. As referências devem ser apresentadas do seguinte modo:

Revistas [1] Dinis da Gama A, Perdigão J, Ministro A, Evangelista A, Damião A, Garcia Alves A. The utilization of the “simplified technique” in the simultaneous management of

independent thoracic and abdominal aortic aneurysms. A clinical report. RevPort Cir Cardiotorac V 2009;3:149 155.

Livros [2] Antunes M J. A Doença da Saúde. Lisboa: Quetzal 2001:167- 176. Vários Autores[3] Fragata J, Martins L. Como evitar o erro em Medicina. Em: Fragata J, Martins L, autores. O Erro em Medicina. Lisboa:Almedina, 2008:313-348. Publicações Online (O DOI é referência obrigatória e a única necessária para citações de artigos de publicações online)

Publicações Online (O DOI é referência obrigatória e a única necessária para citações de artigos de publicações online)[4] Azevedo O, Almeida J, Nolasco T, Medeiros R, Casanova J, Bartosch C, Almeida J, Pinho P. Massive right atrial myxoma presenting as syncope and exertional dyspnea: case report.Cardiovascular Ultrasound doi:10.1186/1476-7120-8-23.

E. TABELAS
As tabelas devem ser numeradas de acordo com a sequencia de aparecimento no texto, e enviadas num ficheiro conjunto a parte do texto, em formato Word. Devem incluir numero e cabeçalho, assim como legenda se necessária.

F. CABECALHO E LEGENDAS DE FIGURAS
O cabeçalho e legendas de figuras devem ser entregues num ficheiro conjunto a parte do texto, em formato Word, mencionando o numero correspondente ao ficheiro de imagem enviado.

G. FIGURAS
As figuras devem ser numeradas de acordo com a sequencia de aparecimento no texto, e enviadas em ficheiros individuais, referenciando o respectivo numero. Apenas são aceites ficheiros em formato .tiff com um mínimo de 300dpi.

SUBMISSAO ELECTRONICA
A submissão electrónica de manuscritos deve ser realizada para:

manuscritos.revista@spcctv.pt

Apenas são consideradas validas as submissões que cumpram as regras anteriormente descritas. Após a submissão, os Editores confirmarão a boa recepção do manuscrito junto do autor correspondente.

MANUSCRITOS ACEITES PARA REVISAO
Os manuscritos revistos devem ser enviados convenientemente titulados – revisão1, revisão2, etc, incluindo novas figures e tabelas caso necessário. Os comentários dos editores e/ou revisores devem ser discutidos ponto a ponto numa carta anexa e as alterações propostas discutidas. As alterações devem ser visíveis utilizando a função "track changes" do Word.